Pharmacodynamic and pharmacokinetic analysis of CNS-active constitutional isomers of valnoctamide and sec-butylpropylacetamide — Amide derivatives of valproic acid

Hafiz Mawasi a,1, Tawfeeq Shekh-Ahmad a,1, Richard H. Finnell b, Bogdan J. Wlodarczyk b, Meir Bialer a,c,⁎

a School of Pharmacy, Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem 91120, Israel
b Department of Nutritional Sciences, Dell Pediatric Research Institute, The University of Texas at Austin, Austin, TX, USA
c David R. Bloom Center for Pharmacy, The Hebrew University of Jerusalem, Jerusalem 91120, Israel

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Constitutional isomers

A B S T R A C T

Valnoctamide (VCD) and sec-butylpropylacetamide (SPD) are CNS-active closely related amide derivatives of valproic acid with unique anticonvulsant activity. This study evaluated how small chemical changes affect the pharmacodynamics (PD; anticonvulsant activity and teratogenicity) and pharmacokinetics (PK) of three constitutional isomers of SPD [sec-butylisopropylacetamide (SID) and tert-butylisopropylacetamide (TID)] and of VCD [tert-butylethylacetamide (TED)]. The anticonvulsant activity of SID, TID, and TED was comparatively evaluated in several rodent anticonvulsant models. The PK–PD relationship of SID, TID, and TED was evaluated in rats, and their teratogenicity was evaluated in a mouse strain highly susceptible to teratogen-induced neural tube defects (NTDs). sec-Butylisopropylacetamide and TID have a similar PK profile to SPD which may contribute to their similar anticonvulsant activity. tert-Butylethylacetamide had a better PK profile than VCD (and SPD); however, this did not lead to a superior anticonvulsant activity. sec-Butylisopropylacetamide and TED did not cause NTDs at doses 4–7 times higher than their anticonvulsant ED50 values. In rats, SID, TID (ip), and TED exhibited a broad spectrum of anticonvulsant activity. However, combined anticonvulsant analysis in mice and rats shows SID as the most potent compound with similar activity to that of SPD, demonstrating that substitution of the isobutyl moiety in the SPD or VCD molecule by tert-butyl as well as a propyl-to-isopropyl replacement in the SPD molecule did not majorly affect the anticonvulsant activity.

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1. Introduction

Valnoctamide (VCD, Fig. 1) is a CNS-active chiral constitutional isomer of valpromide (VPD, Fig. 1), the corresponding amide of valproic acid (VPA) [1–3]. Unlike VPD that in humans acts as a prodrug to VPA, VCD acts as a drug on its own with minimal biotransformation to its corresponding acid, valnoctic acid (VCA) [1,4–6]. sec-Butylpropylacetamide (SPD, Fig. 1) is a one-carbon homologue of VCD currently in the preclinical stage that has unique activity against status epilepticus and organophosphate neuronal damage [7–9]. Both VCD and SPD (Fig. 1) possess two stereogenic carbons in their structure and exist as racemic mixture of 4 stereoisomers.

Valnoctamide (racemate) was commercially available as an anxiolytic drug (Nirvanil®) in several European countries from 1964 until...
Racemic VCD and racemic SPD have a wide spectrum of anticonvulsant activity, and their ED₅₀ values are 2–16 times (depending on the model) more potent than those of VPA [7,9,13–15]. Valnoctamide (65 mg/kg, ip) also provided full protection in the pilocarpine-induced status epilepticus (SE) rat model when administered at seizure onset. However, in contrast to its one-carbon homologue, SPD, VCD lost its behavioral SE protection when administered (80 mg/kg) 30 min after seizure onset [14], but it did block pilocarpine-induced electrographic SE at a higher dose (180 mg/kg) [8]. Following a single dose (600 mg/kg, ip) at day 8.5 of gestation, VCD and SPD and their individual stereoisomers failed to exert any significant teratogenic effect in Swiss Vancouver (SWV)/Fnn mice, an inbred mouse strain that is highly susceptible to VPA-induced teratogenicity [9,14].

All studies so far have focused on VCD and SPD and their individual stereoisomers [7,9,13,14]. The current study comparatively evaluated the pharmacodynamics (PD; anticonvulsant activity and teratogenicity) and pharmacokinetics (PK) of three constitutional isomers of SPD [sec-butylpropylacetamide (SPD), sec-butylisopropylacetamide (SID), and tert-butylethylacetamide (TED)] and of VCD [tert-butylethylacetamide (TED)]. Tert-Butylethylacetamide and TID are the two new constitutional isomers of VCD and SPD, respectively, where the sec-butyl moiety was substituted with tert-butyl. sec-Butylisopropylacetamide is an SPD constitutional isomer where SPD’s n-propyl moiety was replaced by isopropyl. The study also aimed to explore the impact of small chemical changes on the unique anticonvulsant activity of VCD and SPD.

2. Materials and methods

2.1. Animals and test substances used for seizure testing

Male and female albino CF1 mice (18–25 g, Charles River, Portage, MI) and male albino Sprague–Dawley rats (100–150 g, Charles River, Wilmington, MA) were used as experimental animals. Animals were housed in an Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC)-accredited temperature- and humidity-controlled facility and maintained on a standard 12 h/12 h light–dark (lights on at 06:00) cycle with free access to standard laboratory chow (Prolab RMH 3000, Charles River, Wilmington, MA, USA) and water ad libitum. All animal experiments were performed in accordance with the guidelines set by the National Institutes of Health and the University of Utah Institutional Animal Care and Use Committee (IACUC). All animals were allowed free access to both food and water except when they were removed from their cages for the experimental procedure. Except for the kindling studies, animals were used once. All animals were euthanized in accordance with the Institute of Laboratory Resources policies on the humane care of laboratory animals. In 0.5% methylcellulose, TID, SID, or TED was administered (ip or po) in a volume of 0.04 mL/10 g body weight to rats.

2.2. Biological testing/anticonvulsant activity

2.2.1. Pharmacokinetic studies: analysis of TID, SID, and TED in plasma

The plasma concentrations of each compound were quantified by a GC/MS assay. Plasma (200 μL) was added to the test tubes, followed by 25 μL of methanol and 25 μL of internal standard solution [α-fluoro-2,2,3,3-tetramethylcyclopropanecarboxamide (α-F-TMCD) 250 μg/mL in methanol] [14], and the tubes were thoroughly vortexed. Chloroform (2 mL) was used for the extraction of the compounds. The dry residues obtained after evaporation of 1.8 mL chloroform were reconstituted with 50 μL methanol, of which 1 μL was injected into the GC/MS apparatus. The temperature program was as follows: injector temperature of 200 °C, initial temperature of 60 °C for 5 min, gradient of 15 °C/min until 180 °C, gradient of 20 °C until 310 °C, and hold time of 1 min. The MS parameters were set as follows: source temperature of 200 °C, transfer line of 280 °C, and positive ion monitoring using EI-MS at 70 eV. The pressure of the carrier gas, helium, was set.
Table 1

Anticonvulsant activity (ED$_{50}$) and neurotoxicity (TD$_{50}$) of TED, TID, and SID in comparison to their respective constitutional isomers (VCD and SPD) following ip and oral administration to rats.$^a$

<table>
<thead>
<tr>
<th>Anticonvulsant test</th>
<th>ED$_{50}$ (95% confidence interval) (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SPD</td>
</tr>
<tr>
<td>po administration</td>
<td></td>
</tr>
<tr>
<td>Maximal electroshock seizure (MES)</td>
<td>29 (18–53)</td>
</tr>
<tr>
<td>Metrazol-induced seizure (scMet)</td>
<td>18 (13–25)</td>
</tr>
<tr>
<td>Neurotoxicity (TD$_{50}$)</td>
<td>154 (124–192)</td>
</tr>
<tr>
<td>ip administration</td>
<td></td>
</tr>
<tr>
<td>Maximal electroshock seizure (MES)</td>
<td>20 (15–27)</td>
</tr>
<tr>
<td>Pilocarpine-induced status epilepticus (0 min)</td>
<td>8/8 protected</td>
</tr>
<tr>
<td>at 65 mg/kg$^e$</td>
<td>at 65 mg/kg</td>
</tr>
<tr>
<td>Pilocarpine-induced status epilepticus (30 min)</td>
<td>84 (62–103)$^f$</td>
</tr>
<tr>
<td>Neurotoxicity (TD$_{50}$)</td>
<td>49 (43–55)</td>
</tr>
</tbody>
</table>

$^a$ Four to 8 rats were used to determine the ED$_{50}$ and TD$_{50}$ values.
$^b$ Not determined.
$^c$ Data are taken from ref. [7].
$^d$ Data are taken from ref. [18].

at 5 psi. For EI analysis, the ionization energy was 70 eV with a source pressure of 10$^{-5}$ Torr. Retention times of SID, TED, TID, and the internal standard were 12.5, 12.7, 11.2, and 10.1 min, respectively. Calibration curves were constructed for each analytical run and were linear on the concentration range between 100 and 100 μg/mL.

2.2.2. Calculation of pharmacokinetic (PK) parameters

The PK parameters of SID, TED, and TID were calculated by noncompartmental analysis based on statistical moment theory using PK software Phoenix WinNonlin Tripos L.P. version 6.3 (Pharsight Co., Mountain View, CA) as previously described [7,9,14].

2.2.3. Anticonvulsant tests in animals

The antiepileptic potential of the tested compounds was established in mice and/or rats using the following seizure models: maximal electroshock (MES), chemically induced shock with subcutaneous pentylenetetrazole (metrazol) (scMet), bicuculline (scBIC), picrotoxin (scPIC), the 6-Hz psychomotor test, the corneally kindled mouse, Frings audiogenic seizure mouse, and rat pilocarpine tests. In the MES test, 60 mg/kg of alternating current was delivered through corneal electrodes for 0.2 s. Four to 8 mice or rats were used to determine the ED$_{50}$ and TD$_{50}$ values. During the time of administration of the test substance, a drop of 0.5% tetracaine in saline is applied to the eyes of the animals. Animals were restrained by hand during administration of the electrical stimulus and then released for observation of the seizure throughout its entire course. A test substance/dose that is able to abolish the hind limb tonic extensor component of the seizure, indicating prevention of the MES-induced seizure spread, is considered “active”. Tonic extension was considered abolished if the hind limbs were not fully extended at 180° to the plane of the body.

In the scMet seizure test, a convulsant dose of pentylenetetrazole was injected subcutaneously (85 mg/kg in mice) at the time to peak effect of the test substance, followed by observation of seizure occurrence. Absence of seizures indicates that the tested compound/dose can elevate the pentylenetetrazole seizure induction threshold. Systemic administration of pilocarpine, a cholinergic agonist, has been used to induce status epilepticus. This seizure state is clinically defined as continuous seizure activity or multiple seizures without regaining consciousness lasting more than 30 min. To determine if a test substance can prevent acute pilocarpine-induced status epilepticus, candidate drugs were administered to male Sprague–Dawley rats via the ip route, followed by administration of a challenge dose of pilocarpine immediately (0 min) and 30 min after treatment with a candidate drug. The outcome measures were “protection” or “no protection” from epileptic seizures. In addition, morbidity was also determined 24 h after each test was completed. Quantitative determination of the protective effect was undertaken for compounds found to possess significant protection. This included calculations of the peak time response as well as determination of ED$_{50}$ and 95% confidence limits.

2.2.4. Minimal behavioral toxicity tests

Minimal toxicity was identified in rats and mice as minimal motor impairment (MMI) as determined by overt evidence of ataxia, abnormal gait, and stance.

2.2.5. Teratogenicity

For this study, the highly inbred SWV/Fnn mouse strain with a known susceptibility to AED-induced neural tube defects (NTDs) was used according to the previously published procedure [16,17]. Dams were allowed to mate overnight with male mice and were examined

Table 2

Anticonvulsant activity and neurotoxicity of TED, TID, and SID in comparison to their respective constitutional isomers (VCD and SPD) following ip administration to mice.$^a$

<table>
<thead>
<tr>
<th>Anticonvulsant test</th>
<th>ED$_{50}$ (95% confidence interval) (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SPD</td>
</tr>
<tr>
<td>6 Hz 32 mA</td>
<td>27 (24–30)</td>
</tr>
<tr>
<td>6 Hz 44 mA</td>
<td>45 (40–49)</td>
</tr>
<tr>
<td>Maximal electroshock seizure (MES)</td>
<td>71 (55–90)</td>
</tr>
<tr>
<td>Metrazol-induced seizure (scMet)</td>
<td>62 (47–71)</td>
</tr>
<tr>
<td>Bicuculline-induced seizure (scBIC)</td>
<td>94 (87–103)</td>
</tr>
<tr>
<td>Picrotoxin-induced seizure (scPIC)</td>
<td>17 (9–28)</td>
</tr>
<tr>
<td>Corneally kindled mouse</td>
<td>39 (31–45)</td>
</tr>
<tr>
<td>Frings audiogenic seizures</td>
<td>20 (18–22)</td>
</tr>
<tr>
<td>Neurotoxicity (TD$_{50}$)</td>
<td>114 (100–134)</td>
</tr>
</tbody>
</table>

$^a$ Four to 8 rats were used to determine the ED$_{50}$ and TD$_{50}$ values.
$^b$ Not determined.
on the following morning for the presence of vaginal plugs. The onset of gestation was set at 1 a.m. of the previous night. On gestational day 8.5, pregnant females received a single ip injection (10 $\mu$L per gram of body weight) of sodium valproate at a dose of 1.1, 1.8, or 2.7 mmol/kg or TID, SID, and TED at a dose of 1.8 or 2.7 mmol/kg. A 25% Cremophor EL water solution was injected ip to dams constituting the control group. On gestation day 18.5, the dams were euthanized by CO2 asphyxiation, the abdomen opened, and the gravid uteri removed. The locations of all viable, dead, and resorbed fetuses were recorded, and the fetuses were grossly examined for the presence of exencephaly. For statistical purposes, either ANOVA with Tukey’s posttest multiple comparison (fetus weight) or contingency table analysis with Fisher’s exact test (number of resorptions and NTDs) was performed. The p-value was set at 0.05.

2.3. Methods

A gas chromatography–mass spectrometry (GC/MS) assay was performed on a HP5890 series II GC equipped with a Hewlett-Packard MS engine (HP5989A) single quadrupole mass spectrometer, HP7673 autosampler, HP MS-DOS Chemstation, and HP-5MS capillary column (0.25 $\mu$m × 15 m × 0.25 mm). The temperature program was as follows: injector temperature of 180 °C, initial temperature of 60 °C for 5 min, gradient of 20 °C/min until 180 °C, gradient of 10 °C/min until 300 °C, and hold time of 3 min. The MS parameters were set as follows: source temperature of 180 °C, transfer line temperature of 280 °C, and positive ion monitoring using electron ionization–mass spectrometry (EI-MS) at 70 eV. The molecular ion and the five most pronounced ions are provided. Elemental analyses were preformed on a 2400-2 Perkin-Elmer CHN analyzer. The C, H, and N analyses of all newly synthesized compounds were within ±0.4 of theoretical values and, thus, were considered satisfactory.

2.4. Water solubility and ClogP calculations

The solubility of SID, SPD, TED, TID, and VCD in water and various other solvents was determined by adding gradually 10–100 mg of each compound to 1 mL of double-distilled water or any other solvent until the compound precipitated. The solution was stirred for 2 h. At the end of the 2-h period, the sample was centrifuged and 1-μL aliquots were taken for the GC analysis. ClogP was calculated by utilizing the ChemDraw Ultra version 8 software.

3. Results

3.1. Chemistry

The syntheses of SID, TID, and TED were previously described by Kaufmann et al. [18]. Briefly, the starting material for SID was 3-methylvaleric acid and for TED and TID, dimethylbutyric acid. The acids were converted to their corresponding enolates by LDA, followed by substitution of a hydrogen atom on the $\alpha$-carbon by the appropriate alkyl using specific alkyl iodide. The carboxylic acids were treated with thionyl chloride in order to produce the corresponding acyl chloride followed by treatment with NH4OH. The chemical structures of the synthesized amides were identified by $^1$H NMR GC–MS, while purity was established using elemental analysis.

3.2. Time to peak effect (TPE) of SID, TID, and TED and determination of their median effective (ED$_{50}$) or behavioral toxic (TD$_{50}$) dose

All quantitative in vivo anticonvulsant/behavioral neurotoxicity studies were conducted at time to peak effect (TPE) values previously determined in a qualitative analysis. The TPE of SID, TED, and TID was 0.25 h following ip and oral administration. Groups of 4–8 mice or rats were tested with various doses until at least two points were established between the limits of 100% protection or minimal toxicity and 0% protection or minimal toxicity. The dose of drug required to produce the desired endpoint in 50% of animals (ED$_{50}$ or TD$_{50}$) in a 48-h test, the 95% confidence interval, the slope of the regression line, and the SEM of the slope were then calculated by a computer program based on the method described by Finney [19].

3.3. Anticonvulsant efficacy of SID, TED, and TID in seizure and epilepsy rodent models

The anticonvulsant activity of SID, TID, and TED in comparison to their respective isomers (SPD and VCD) is depicted in Tables 1 (rats) and 2

<table>
<thead>
<tr>
<th>Solvent</th>
<th>SPD</th>
<th>TID</th>
<th>SID</th>
<th>VCD</th>
<th>TED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1.5</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Saline:PG:EtOH (5:4:1)</td>
<td>5</td>
<td>16</td>
<td>33</td>
<td>50</td>
<td>31</td>
</tr>
<tr>
<td>PG:water:EtOH (4:5:1)</td>
<td>27</td>
<td>17</td>
<td>33</td>
<td>50</td>
<td>31</td>
</tr>
<tr>
<td>PG:water:EtOH (5:4:1)</td>
<td>50</td>
<td>22</td>
<td>66</td>
<td>80</td>
<td>63</td>
</tr>
<tr>
<td>ClogP</td>
<td>2.2</td>
<td>2.0</td>
<td>2.1</td>
<td>1.7</td>
<td>1.6</td>
</tr>
</tbody>
</table>

PG—propylene glycol and EtOH—ethanol.

ClogP was calculated by utilizing the ChemDraw Ultra version 12 software.

![Fig. 2. Plasma concentration–time plots of SID (50 mg/kg), TID (50 mg/kg), and TED (70 mg/kg) following ip administration to rats. Each time point represents a mean from three rats with % coefficient of variation (CV) of 20–30%.

Table 3

<table>
<thead>
<tr>
<th>Solvent</th>
<th>SPD</th>
<th>TID</th>
<th>SID</th>
<th>VCD</th>
<th>TED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1.5</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Saline:PG:EtOH (5:4:1)</td>
<td>5</td>
<td>16</td>
<td>33</td>
<td>50</td>
<td>31</td>
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<td>31</td>
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<td>50</td>
<td>22</td>
<td>66</td>
<td>80</td>
<td>63</td>
</tr>
<tr>
<td>ClogP</td>
<td>2.2</td>
<td>2.0</td>
<td>2.1</td>
<td>1.7</td>
<td>1.6</td>
</tr>
</tbody>
</table>

PG—propylene glycol and EtOH—ethanol.

ClogP was calculated by utilizing the ChemDraw Ultra version 12 software.
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Butylethylacetamide had a different PK profile (Table 4) and SID was rather short and ranged between 0.6 and 0.8 h.

ED50 values. The plasma concentration chosen for the PK study were the intermediate doses among the various isomers, their lipophilicity expressed as ClogP.

VCD and their individual stereoisomers [7,9,14].

Significant. In contrast to VPA, SID and TED did not cause a statistically significant increase of NTDs at doses of 141 and 283 mg/kg (Table 4).

However, following oral administration, TED was found to be less potent than VCD in the MES test but was more potent at the scMet dose. TED's PK profile compared to all other closely related investigated compounds did not translate into a better anticonvulsant activity. TED's constitutional isomer in which the tert-butyl moiety was substituted by n-butyl as well as its nonbranched isomer, octanamide, were previously found to be less potent than VCD [18,24,25]. In contrast, another constitutional isomer of VCD and TED, propylisopropyl acetamide, in which the isobutyl (VCD) or tert-butyl (TED) moiety was replaced by isopropyl and one additional methyl was added to the ethyl side chain (shared by TED and VCD) exhibited a similar wide spectrum of anticonvulsant activity as SPD.
This high E value makes TID susceptible to hepatic first-pass effect after oral administration. Although SID had a similar clearance value as TID (Table 4), its solubility was 2–3 times higher than that of TID. The better solubility of SID may contribute to its similar rat MES and scMet E50 values following oral and ip administration (Table 1). In the pilocarpine-induced SE model, SID was equipotent to SPD at 0 and 30 min after seizure onset but was more potent than TID, TED, and VCD. Although SID, SPD, TED, TID, and VCD have similar lipophilicity, SPD had the highest ClogP value and the lowest water solubility (Table 3), a fact that may contribute to its wide and potent spectrum of anticonvulsant activity.

Since numerous commercially available AEDs are teratogenic, it is essential to develop new AEDs that are not teratogenic [27,28]. This is particularly crucial for VPA as on November 21st, 2014, theEMA’s Coordination Group for Mutual Recognition and Decentralized Procedures (CMDh) decided to strengthen the warning on the use of VPA in women and girls because of the risk of malformation and developmental problems in children exposed to VPA in the womb that might be associated with autistic spectrum disorder and childhood autism [29]. In contrast to VPA, SID and TED did not cause a statistically significant increase of NTDs at doses of 141 and 283 mg/kg (Table 5). These doses are 4–7 times higher than their anticonvulsant ED50 values. Hereon, we demonstrate that SID and TED failed to induce NTDs in SWV mice at the dose of 283 mg/kg (1.8 mmol/kg). Thus, SID and TED are superior to VPA not only by exhibiting a more potent anticonvulsant activity but also by their reproductive safety.

Preclinical strategies in new drug (AEDs) discovery used to identify potential drug candidates include target-based screening, phenotypic screening utilizing animal models, and modifications of existing drugs or natural substances [30,31]. Screening in rodent models has been the engine in AED discovery since phenytoin (1938). Anticonvulsant animal models are effective in identifying new AEDs, are nonselective with respect to the mechanism of action, and provide insight into AEDs’ PK–PD relations including the ability to penetrate the brain and exert a CNS effect [6,32]. Animal models with a similarly high predictive value do not exist in other nonpeptic CNS disorders. In light of the highly heterogeneous nature of seizure disorders in humans and the complexity of seizure phenotypes, it is unlikely that any single animal model will predict the full therapeutic potential of an investigational AED [33]. Consequently, promising investigational new AEDs have to demonstrate activity in a battery of anticonvulsant models that may indicate a wide antiepileptic spectrum in humans. Bialer et al. demonstrated a correlation between AEDs’ ED50 values in the mouse and rat MES models and AEDs’ therapeutic dose and steady-state plasma concentrations in patients with epilepsy [34]. This analysis showed VPA to be the least potent AED in anticonvulsant rodent models. The constitutional isomers of SPD or VCD designed and evaluated in the current study by utilizing the phenotypic approach preserve VPA’s wide anticonvulsant spectrum but are significantly more potent than VPA and, thus, may have a potential to be efficacious in patients who have seizures resistant to VPA.

5. Conclusions

In rats, SID, TID (ip), and TED exhibited a broad spectrum of anticonvulsant activity at nonteratogenic doses. However, combined anticonvulsant analysis in mice and rats shows SID as the most potent compound with similar activity to that of SPD, demonstrating that substitution of SPD’s isobutyl moiety by tert-butyl as well as a propyl-to-isopropyl replacement in the SPD or VCD molecule did not majorly affect the anticonvulsant activity. The lack of significant difference in the anticonvulsant activity of VCD and SPD and their constitutional isomers may indicate that the anticonvulsant activity of these chemically, closely related compounds is due to multiple mechanisms of action. The choice between SID and SPD or TED and VCD could be done after a toxicological analysis coupled with additional pharmacological testing.

Abbreviations

CNS  central nervous system
AED  antiepileptic drug
MES  maximal electroshock seizure
scMet  subcutaneous metrazol
SE  status epilepticus
PI  protective index
VPA  valproic acid

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Disclosure/conflict of interest

Dr. Meir Bialer has received in the last three years speakers’ or consultancy fees from Bial, CTS Chemicals, Desitin, Janssen-Cilag, Johnson & Johnson, Medegenics, Rekah, Sepracor, Teva, UCB Pharma, and Upsher-Smith. Dr. Bialer has been involved in the design and development of new antiepileptic and CNS drugs as well as new formulations of existing drugs.

None of the other authors has any conflict of interest to disclose.

We, the authors, confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References


